The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

Tel: 617-624-5200
Fax: 617-624-5206
www.mass.gov/dph

DEVAL L. PATRICK
GOVERNOR

JOHN W. POLANOWICZ
SECRETARY

CHERYL BARTLETT, RN
COMMISSIONER

Clinical Advisory
Pre-Exposure Prophylaxis for HIV Infection

Using Truvada® (emtricitabine/tenofovir disoproxil fumarate)

Updated: July 2013

On June 14, 2013, the U.S. Centers for Disease Control and Prevention (CDC) published an update to the Interim Guidance for Pre-Exposure Prophylaxis (PrEP). The CDC now recommends that PrEP be considered as one of several prevention options for persons at very high risk for HIV acquisition, including injecting drug users (IDUs).[1] The updated Interim Guidance is available on the Morbidity and Mortality Weekly Report website.

A previous version of this clinical advisory communicated the support of the Massachusetts Department of Public Health (MDPH) for use of Truvada® as PrEP in certain circumstances for HIV-uninfected individuals at high risk of sexually acquired HIV infection. Consistent with the CDC's recommendation, the MDPH supports the use of Truvada® for PrEP for HIV-uninfected injecting drug users. This clinical advisory has been revised to reflect the use of Truvada for PrEP in this population.

Background

On July 16, 2012, the Food and Drug Administration (FDA) approved the use of Truvada®[2] for pre-exposure prophylaxis (PrEP) for HIV-uninfected individuals at high risk of sexually acquired HIV infection. Truvada® (TDF/FTC) is an oral, antiretroviral combination medication that has been approved for the treatment of HIV infection since 2004. Truvada® PrEP offers an evidence-based approach to preventing the acquisition of HIV infection in certain circumstances, and should be considered when those circumstances are present. This clinical advisory provides background on PrEP, evidence of the efficacy of Truvada® as PrEP, guidelines for appropriate use, and sources of further information.

Clinical Trials[3]

Clinical trials in several populations have demonstrated efficacy of Truvada® as pre-exposure prophylaxis to prevent HIV acquisition in HIV-uninfected individuals when combined with counseling about safer sex and other risk reduction methods. In the five clinical trials identified below and described in the table, resistance to FTC and Truvada® was observed in some participants who were unknown to be acutely HIV infected upon initiation or who seroconverted during the trial. Therefore, the potential for HIV drug resistance in persons taking PrEP does exist if acute HIV infection is not ruled out on initiation of PrEP or in cases of PrEP failure, which is most likely due to poor adherence. Poor adherence makes selection of resistant viral strains more likely. Clinical trials included:

iPrEx[4] - a randomized double-blind placebo-controlled multinational study evaluating Truvada®. All subjects received monthly HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections (STI). The Truvada® group achieved a 42% (95% CI: 18% to 60%) reduction of HIV infection as compared to the placebo group.

Partners PrEP[5] - a randomized, double-blind, placebo-controlled three-arm trial conducted in Kenya and Uganda to evaluate the efficacy and safety of TDF alone and Truvada® versus placebo in preventing HIV acquisition by the uninfected partner. The risk reduction for Truvada® relative to placebo was 75% (95% CI: 55% to 87%).

TDF2[6] - a randomized, double-blind, placebo-controlled trial conducted in Botswana with low retention. All subjects received counseling for risk reduction, screening and treatment for STI, and monitoring for adverse events. Overall efficacy was 62% (95% CI: 22% to 83%); however, efficacy was not statistically significant in women.

Fem-PrEP[7] - a randomized, double-blind, placebo-controlled trial of Truvada® combined with counseling in Kenya, South Africa, and Tanzania, which ***failed*** to reduce the rate of HIV infection. Inadequate adherence seems to have undermined the trial's ability to assess efficacy.

Bangkok Tenofivir Study[8] – a randomized, double-blind, placebo-controlled trial conducted to determine the safety and efficacy of tenofovir disoproxil fumarate (TDF) in preventing HIV acquisition among IDUs in Bangkok, Thailand. All subjects received HIV testing, risk reduction counseling, hepatitis B vaccine, monitoring for adverse events, and were offered methadone treatment, condoms, and bleach to clean injection equipment. Female participants were provided with contraceptives. Directly observed therapy (DOT) was available to participants. TDF decreased the risk of HIV infection by 49% (95% CI: 10% -72%).

Clinical Trials: Truvada® as pre-exposure prophylaxis to prevent HIV acquisition

Study	**Population**	**No. and sex of participants**	**mITT* % reduction in HIV incidence (95% CI)**			**TDF blood detection† (95% CI)**
iPrEx	Men who have sex with men	2,499 (100% male)	42% (18%–60%)			92% (40%–99%)
			All	Men	Women	
Partners PrEP	Heterosexual HIV-discordant couples	4,758 couples (38% with female HIV+ partner)	75% (55%–87%)	84% (54%–95%)	66% (28%–84%)	90% (58%–98%)
TDF2	Heterosexual men and women	1,216 (46% female)	62% (22%–83%)	80% (25%–97%)	49% (-21%–81%, NS)	84% (-62%–98%, NS)
FEM-PrEP	Heterosexual women	2,056 (100% female)	NS	NS	NS	NS
Bangkok Tenofivir Study	Injecting drug using men and women	2,413 (20% female)	49% (10-72%)	38% (-18-68%)	79% (17-97%)	70% (2% - 91%)

Abbreviations: mITT = modified intent to treat analysis; CI = confidence interval; NS = finding not statistically significant.

*Excluded only those enrolled participants later found to be infected at randomization and those with no follow-up visit or HIV test.

†The percentage of reduction in HIV incidence among persons with TDF detected in blood, compared with those without detectable TDF.

Important Considerations

In determining the appropriateness of Truvada® as PrEP, the following points should be considered:

- In the absence of an HIV prevention vaccine, Truvada® as PrEP presents an evidence-based prevention option for individuals at high risk of sexual and drug-injection associated acquisition of HIV infection.[9]
- In all of the trials, Truvada® was only one part of a multi-component intervention. Truvada® was combined with relatively intensive, standard behavioral interventions, including risk reduction counseling, condom distribution, frequent HIV and STI testing, prompt STI treatment for newly diagnosed infections, and partner services. In the Bangkok Tenofovir Study, IDUs were provided with bleach to clean drug injection equipment and were offered methadone treatment.
- All but one of the published studies were done in the developing world. The iPrEx trial included men who have sex with men (MSM) and transgender women who have sex with men from the United States along with subjects at similar risk from five other countries.
- All available data on efficacy of PrEP are from clinical trials. Experience outside of a research environment is not available to assess effectiveness in the "real world."
- Adherence to therapy, with adequate blood/tissue levels of active antiviral agents, appears to be the most important determinant of efficacy of Truvada® as PrEP.
- While Truvada® combined with other antiviral medications is well tolerated in patients being treated for HIV infection, the clinical trials reported variable, but in some instances not insignificant, levels of nausea, vomiting, and dizziness (particularly during the initiation phase), as well as some evidence of diminished bone density, serum creatinine changes and abnormal hepatic transaminase values. Adverse events in long term administration of Truvada® in HIV-uninfected individuals have not been fully assessed.
- Among serodiscordant sexual partners, a protection rate of 92- 96% has been demonstrated for the HIV-uninfected partner when the HIV-positive partner is treated early, and effectively with highly active antiretroviral therapy.[10,11] Thus, "treatment as prevention" may be the best option for stable discordant partnerships.

Initiating PrEP

Research studies demonstrating efficacy of oral PrEP have involved particular high-risk populations, concomitant standardized behavioral interventions, fairly intensive support services, and use of Truvada®. Generalizability to other and broader population groups needs further assessment. Use of other antiviral regimens for PrEP cannot be recommended.

In light of the data available from clinical trials and the considerations above, the Massachusetts Department of Public Health (MDPH) identifies certain high risk individuals who may particularly benefit from PrEP and who should be evaluated for their risk for HIV acquisition, as well as readiness and clinical eligibility for PrEP.

PrEP should only be prescribed for persons who are confirmed to be HIV-unifected and:

- Are men who have sex with men (MSM) who currently have repeated unprotected anal and/or vaginal sex
- Are transgender females who currently have repeated unprotected anal and/or vaginal sex
- Are part of a heterosexual, serodiscordant couple wishing to conceive and have been educated about the potential risks/benefits[12]
- Are injecting drug users who are at risk for HIV acquisition through blood exposure secondary to sharing injection equipment
- Use “club drugs” in combination with unprotected sex
- Engage in commercial sex work
- Have recent or repeated diagnoses of syphilis, rectal gonorrhea or rectal chlamydia infection
- Are otherwise deemed appropriate by the prescribing clinician

Once a candidate for PrEP is confirmed at high risk of HIV infection:

- HIV infection should be ruled out by HIV antibody/antigen testing using a 4th generation HIV assay, and/or an HIV RNA test.[13]
- If signs and symptoms suggestive of acute HIV infection are present, rule out acute infection using an RNA test.[14] PrEP should not be initiated until results of this testing is known.
- The PrEP candidate should be screened for STI and viral hepatitis, and immunized against hepatitis A and B (treat chronic hepatitis B if indicated).
- Possible drug interactions should be ruled out.[15]
- Female candidates should be tested for pregnancy. If a patient takes PrEP while pregnant, or becomes pregnant during use of PrEP, providers are encouraged to prospectively and anonymously submit information about the pregnancy to the *Antiretroviral Use in Pregnancy Registry*.[16]
- Confirm creatinine clearance is greater than or equal to 60mL/min (Cockcroft-Gault formula)

Truvada® is excreted via the kidney, and increased drug levels can accumulate with renal impairment. Renal impairment also has been reported with use of TDF. PrEP is not recommended for individuals with creatinine clearance of <60 mL per minute, and all patients treated with Truvada® should have renal function monitored three months after initiation and every six months thereafter while using the PrEP regimen.

Recommended Protocol

Tenofovir disoproxil fumarate (TDF) 300 mg plus emtricitabine (FTC) 200 mg, as one Truvada® tablet, daily. At this time, the MDPH does not recommend intermittent PrEP based on periodic risk behavior due to a lack of efficacy evidence, questions about the ability of most individuals to correctly anticipate their high-risk behaviors, and concern about the development of antiviral resistance.

Follow-up and Discontinuation

The CDC has provided guidance for clinicians on the use of PrEP, with detailed recommendations for follow-up of patients on PrEP.[Error! Bookmark not defined.,17,18] These are:

- *Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men;*
- *Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults; and*
- *Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users.*

Links to these documents are in the Additional Resources section.

Key points for follow-up include ongoing risk reduction and PrEP adherence counseling and ongoing provision of condoms to support sexual risk reduction. Drug injectors should have access to sterile injection equipment, naloxone to prevent overdose, and opioid replacement therapy and/or other drug treatment.

- Every 2-3 months:
  - HIV antibody/antigen testing (4th generation)
  - Pregnancy testing for women
  - Evaluation of adherence and need for more intensive support services
  - Screening/treating for STIs and hepatitis C infection
  - Monitoring serum creatinine 3 months after initiation and every 6 months thereafter
- Report adverse events to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Key indications for discontinuation include:

- If the patient tests positive for HIV infection or suspected acute infection
- If the patient wishes to discontinue treatment
- If the patient is clinically diagnosed with any medical condition or has an abnormal lab value inconsistent with the safe administration of Truvada® as PrEP
- If the patient expresses diminishing commitment to the treatment protocol

REFERENCES

[1] CDC. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users. Morb Mortal Wkly Rep. 2013; 62:463-465.
[2] Emtricitabtine/tenofovir disoproxil fumarate (TDF/FTC, Truvada®, Gilead)
[3] Further details about completed and ongoing clinical trials can be found at www.avac.org/ht/d/sp/i/326/pid/326.
[4] Grant RM, Lama JR, Anderson PL, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010; 363:2587-99.
[5] Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. N Engl J Med 2012; 367:399-410.
[6] Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. N Engl J Med 2012;367:423–34.
[7] Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection Among African Women. N Engl J Med 2012;367:411–22.
[8] Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral Prophylaxis for HIV Infection in Injecting Drug Users in Bangkok, Thailand (the Bangkok Tenofovir Study): A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial. The Lancet 2013. Published online June 13, 2013 http://dx.doi.org/10.1015/S0140-6736(13)61127-7.
[9] The FDA has approved use of Truvada as PrEP for men who have sex with men and heterosexual men and women. Use of Truvada as PrEP for injection drug users currently represents off-label use.
[10] Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV Transmission After Initiation of Antiretroviral Therapy: A Prospective Cohort Analysis. Lancet 2010; 375:2092-8.
[11] Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV Infection with Early Antiretroviral Therapy. N Engl J Med 2011; 365:493-505.
[12] Information concerning the use of Truvada® during pregnancy: http://www.truvada.com/
[13] Development of HIV antibodies can take weeks to months. In June of 2010, a 4th generation HIV diagnostic test was approved by the FDA. This highly sensitive test can detect p24 antigen as well as HIV antibodies thus reducing the time from exposure to detection.
[14] Acute retroviral syndrome symptoms appear 2-6 weeks post HIV exposure in close to 70% of those infected. Symptoms may include: fever, rash, fatigue, pharyngitis, generalized lymphadenopathy, urticaria, myalgia, arthralgia, anorexia, mucocutaneous ulceration, headache, retroorbital pain and neurologic symptoms.
[15] Full prescribing information can be found at http://www.truvada.com.
[16] An Antiretroviral Pregnancy Registry (APR) has been established. Register patients by calling 1-800-258-4263.
[17] CDC. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. MMWR Morb Mortal Wkly Rep. 2011 Jan 28;60(3):65-8.
[18] CDC. Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults. MMWR Morb Mortal Wkly Rep. 2012 Aug 10;61:586-9.

ADDITIONAL RESOURCES

- Truvada® was approved by the FDA with a Risk Evaluation and Mitigation Strategy (REMS). A detailed description of this strategy as well as a list of educational resources for health care professionals is available at https://www.truvadapreprems.com.
- The CDC offers current PrEP information and links to additional resources at www.cdc.gov/hiv/prep including:
    - Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults
    - Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men
    - Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users
- Massachusetts Department of Public Health at www.mass.gov/dph/aids
- Project Inform at http://www.projectinform.org/prep/
- U.S. Department of Health and Human Services Health Resources and Services Administration *Guide to HIV/AIDS Clinical Care* http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11